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META-ANALYSIS OF PLACEBO-CONTROLLED STUDIES OF TROSPIUM CHLORIDE 20 MG BID IN PATIENTS WITH DETRUSOR OVERACTIVITY

Aims of Study

The primary objective of this meta-analysis was the systematic and quantitative review of the results of two independent placebo-controlled studies of trospium chloride (TCl) in patients with detrusor overactivity (1, 2) with regard to efficacy and safety.

Methods

The data of two multicentre, placebo-controlled, randomised, double-blind clinical trials of 20 mg TCl bid (Spasmolyt®) given for 3 weeks in adult patients with detrusor overactivity were included in the meta-analysis. Main exclusion criteria were stress incontinence, closed-angle glaucoma, tachydysrhythmias, mechanical stenoses of the gastrointestinal tract or urinary outlet obstruction, myasthenia gravis, allergies, and other severe diseases. Concomitant treatment with other anticholinergics, antidepressants, α-blockers and β-sympathomimetics were not allowed. The effect of TCl on detrusor function was investigated by means of cystometric urodynamic measurements (according to the ICS Guidelines). Primary efficacy variables were the 'maximum bladder capacity' and the 'volume at first unstable contraction'. Secondary variables included the 'volume reached at maximum contraction', 'maximum detrusor pressure at first unstable contraction', 'bladder compliance', 'residual urine volume', 'detrusor pressure at maximum flow' and a 'global assessment of efficacy' by the investigator and the patient. The urodynamical variables were measured at baseline (Day 0) and after 3 weeks of study treatment (Day 21).

Safety was evaluated based on adverse events (AEs), physical examinations, ECGs, and the clinical laboratory tests at the end of the treatment relative to the baseline values.

The stratified Wilcoxon-Mann-Whitney test with studies as strata was carried out in the statistical analysis. The treatment effect between TCl and placebo was estimated by the method of Hodges-Lehmann for the median differences. Additionally, the corresponding 95% confidence intervals were calculated.

Results

A total of 517 patients were included in this meta-analysis (TCl: n=314, placebo n=203, reflecting the different allocation ratios of 2:1 and 1:1 in the two studies).The demographic data and the baseline values of the urodynamical variables were well balanced between the treatment groups. The treatment effect for the changes from baseline of the 'maximum bladder capacity' was more pronounced in the TCl group compared to placebo (mean difference +61.1 ml, Hodges-Lehmann estimator +52.0 ml, $p<0.0001$, 95% ci: +32 ml, +71 ml). Also, there were significant results favouring TCl treatment in comparison to placebo with regard to the 'volume at first unstable contraction' (mean difference +62.2 ml, Hodges-Lehmann estimator +48.0 ml, $p=0.0001$, 95 % ci: +28 ml, +68 ml). Furthermore, a statistical significant difference between the two treatments was seen in the 'volume reached at maximum contraction', whereas no pronounced treatment differences were found in the other urodynamical efficacy variables. In the investigator's global assessment of efficacy, more patients of the TCl group (43.1%) were 'cured' or had 'improved markedly' at the end of the study than in the placebo group (23.0%, $p<0.0001$).

An AE was observed in 35.7% of the TCl patients compared to 38.9 % of the placebo patients ($p=0.46$). Dry mouth was the most frequent single AE reported (TCl: 14.0%; placebo: 8.4%, $p=0.052$). The statistical analysis revealed that CNS disorders occurred significantly less frequently in the TCl group (11.1%) than in patients treated with placebo (17.7%, $p=0.033$). Two probably drug-related serious AEs (SAEs) were observed in the active treatment group (urinary retention). A possibly drug-related urinary retention was found in the placebo group as a SAE. There were no clinically relevant changes in laboratory variables; similarly, vital signs, physical examinations, and ECGs caused no safety concerns.

Conclusions

This meta-analysis confirmed that 20 mg TCl bid given for three weeks is an effective option in patients with detrusor overactivity. A marked effect of TCl on detrusor tonus and functions of the bladder could be observed in ‘maximum bladder capacity’, ‘volume at first unstable contraction’, and ‘volume reached at maximum contraction’ compared to placebo. Furthermore, with an incidence of AEs comparable to placebo TCl is an effective treatment option with a favourable safety profile.

(1) J Clin Res 1998; 1: 439-51.
(2) BJU International 2000, 85: 659-664.